REMARKS

Claims 29-34 are currently pending in the application. In order to advance prosecution, Applicants have amended claims 29, 31, 33 to more particularly point out and distinctly and clearly claim their invention. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims are made in order to expedite the issuance of the claims. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

Discussion of the 35 U.S.C. § 112, paragraph 2 Rejection

Claims 29-32 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because claim 29 refers to treating a subject with an anti-EGFR antibody when HER3 levels are "low." Although not acquiescing to this ground of rejection or the Examiner's reasoning supporting the rejection, Applicants have amended claim 29 to recite "having an OD less than 9 when determined by quantitative immunohistochemistry." Applicants respectfully contend that this amendment overcomes the asserted grounds of rejection. Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

Discussion of the 35 U.S.C. § 112, paragraph 1 Rejection

Claims 30, 32 and 34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not set forth in such a way as to enable one skilled in the art to make and/or use the invention.

Applicants respectfully point out that U.S. Patent No. 6,233,883 (the '883 patent) has been expressly incorporated by reference in the instant application (page 4 and line nos. 16-18). The '883 patent teaches hybridoma E7.6.3 and ABX-0303 (also referred to as ABX-EGF or panitumumab, which is the active ingredient of Vectibix™). *See, e.g.*, the '883 patent, col. 28, line 62-col. 29, line36 and Figures 29-32. The Office has acknowledged this, but has contended that the '883 patent does not *claim* hybridoma E7.6.3 or ABX-0303. The Patent Office also contends that the present claims are drawn to methods that require the use of a specific antibody, and that the disclosure of the '883 patent does not provide the entire sequence of this specific antibody. And, even though the Patent Office acknowledges that the Yang *et al.* reference, relied on by the Patent Office for a rejection under 35 U.S.C. § 103, teaches the ABX-EGF antibody, and that the antibody was available at the time the instant application was filed, the Patent Office contends that there is no evidence that the restrictions on the availability of ABX-EGF have been removed. Applicants respectfully traverse the rejection.

Contrary to the assertions by the Patent Office, the ABX-0303 antibody was taught and claimed by the '883 patent, and is currently available as the active ingredient of a treatment for EGFR-expressing metastatic colorectal carcinoma. An Investigational New Drug (IND) application was filed with the FDA on May 15, 1999 for Vectibix™, which contains the active ingredient panitumumab or ABX-0303. *See* U.S. Patent No. 6,235,883 File History Paper No. 30 (Application for Extension of Patent Term Under 35 U.S.C. § 156), at 2 & 5, attached hereto as Exhibit A. A Biologics Licensing Application (BLA) was initially submitted on December 15, 2005, and was approved and licensed under the Department of Health and Human Services U.S. License No. 1080, on

September 27, 2006. *See id.* at 5. The '883 patent claims the active ingredient of Vectibix™, ABX-0303. *See id.* at 7. For example, at least claim 15 is the applicable claim directed to the approved product. *See id.* at 4. Claim 15 recites "An isolated antibody that is capable of binding epidermal growth factor comprising a heavy chain variable region comprising a contiguous sequence from CDR1 through CDR3 as represented in SEQ ID NO:37." *See id.* Vectibix™ is currently indicated as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. *See* Vectibix™ package insert, attached hereto as Exhibit B. Therefore, it is clear that not only did the '883 patent claim the ABX-0303 antibody, but that the antibody is well known in the art, and is available as approved by the Food and Drug Administration.

Furthermore, the Patent Office apparently does not disagree that Yang, et al. teaches the production, characterization, and use of ABX-EGF, which is the ABX-0303 antibody of the instant application. Applicants reiterate that the production of the ABX-0303 antibody of the instant application is well known to those of skill in art, and thus claims 30, 32, and 34 do not require undue experimentation and are fully enabled.

Finally, Applicants again note that the present claims are not drawn to the antibody ABX-0303, to hybridoma E7.6.3, or to the antibodies produced by hybridoma E7.6.3. Instead, the present claims are drawn to methods of using the ABX-0303 antibody. Applicants recognize that claims to a method requiring a reagent that is unknown or unavailable can fail to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. *University of Rochester v. G.D. Searle*, 69 U.S.P.Q.2d 1886 (Fed. Cir.

2004). However, that is not the case here. As established above, the '883 patent claims the very antibodies for which a use is described in the present invention. The '883 patent is entitled to the presumption that it is valid and its claims (including at least claim 15 encompassing the ABX-0303 antibody) are enabled. Thus, the *use* of the patented antibodies in the present invention cannot fail to satisfy the enablement requirement based on the availability status of these antibodies.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Discussion of the 35 U.S.C. § 103 Rejections

Claims 29, 31 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herbst in view of Xia. The Applicants respectfully traverse the rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

The Patent Office does not take issue with the fact that Xia and Herbst do not individually teach or suggest the present invention. In fact, the Patent Office does not appear to disagree that the combination of Xia and Herbst would suggest to one skilled in the art to treat a patient with high levels of EGFR, not a patient with low levels of HER3. Rather, the Patent Office contends that the present claims read on methods of treating a subject "when HER3 expression levels are low," and that the claims do not recite a separate step of categorizing patients and then choosing a certain category to treat. The Patent Office concludes that the present claims include methods "where the level of HER3 was not necessarily the deciding factor."

In response, Applicants respectfully disagree, and contend that the claims do, in fact, require a method of categorizing subjects based on the expression level of HER3, *i.e.*, when HER3 expression levels are low. However, in the interest of expediting issuance of the claims, Applicants have amended claim 29 to recite treating a subject "if HER3 expression levels are detected having an OD less than 9 when determined by quantitative immunohistochemistry," thereby obviating this rejection. Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herbst in view of Xia and further in view of Yang. The Applicants traverse the rejection.

The Patent Office contends that this rejection is maintained for the same reasons given for the rejection of claims 29, 31, and 33 over Herbst and Xia, with the further acknowledgement that Herbst and Xia do not teach the use of ABX-0303. However, as indicated above, in the interest of expediting issuance of the claims, Applicants have amended claim 29 to recite treating a subject "if HER3 expression levels are detected having an OD less than 9 when determined by quantitative immunohistochemistry." The further citation of Yang does not cure the deficiencies of Xia and Herbst. Therefore, Applicants contend that the amendment to claim 29 also obviates this rejection. Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Based on all of the above, the Applicants believe the claims are now allowable. If there are any questions or comments regarding this response, the Patent office is encouraged to contact the undersigned agent as indicated below.

Respectfully submitted,

Date: March 20, 2008

/Andrew W. Williams/
Andrew W. Williams
Registration No. 48,644

McDonnell Boehnen Hulbert & Berghoff, LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

EXHIBIT A

180 DAC

PATENT
Attorney Docket No.: 06843.0111

#30

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 6,235,883)
)
Issued: May 22, 2001)
)
To: Aya Jakobovits, Xiao-Dong Yang,)
Michael Gallo, and Xiao-Chi Jia)
)
Assignee: Amgen Fremont Inc.)
)
For: HUMAN MONOCLONAL ANTIBODIES TO)
EPIDERMAL GROWTH FACTOR RECEPTOR)

MAIL STOP PATENT EXT.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Applicant, Amgen Fremont Inc., represents that it is the assignee of the entire interest in and to United States Patent No. 6,235,883 granted to Aya Jakobovits, Xiao-Dong Yang, Michael Gallo, and Xiao-Chi Jia on the 22nd day of May 2001, for Human Monoclonal Antibodies to Epidermal Growth Factor Receptor. An assignment from the inventors to Abgenix, Inc. was recorded at Reel 009216, Frame 0322 on May 5, 1988. Abgenix, Inc. was then acquired by Amgen, Inc., resulting in Abgenix, Inc. now being known as Amgen Fremont Inc. The merger/change of name document was filed in the U.S. Patent and Trademark Office for recordation on November 21, 2006. Copies of the assignment document from the inventors and the merger/change of name document are enclosed in Attachment A.

11/24/2006 TBESHAH1 00000036 6235883
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By the Power of Attorney enclosed herein (Attachment B), Applicant appoints Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Customer No. 22,852, including Charles E. Van Horn, as its attorneys, with regard to this application for extension of the term of U.S. Patent 6,235,883 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Information Required Under 37 C.F.R. § 1.740

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which follows the requirements of § 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product is Vectibix™, which contains the active ingredient panitumumab. Panitumumab is a tetramer containing two heavy chains and two light chains of amino acids, with disulfide bridges. Sugar residues are also attached to the heavy chains. The single-letter amino acid sequences of the heavy chain and light chain are shown below:

Vectibix Heavy Chain

```
  1 QVQLQESGPG LVKPSETLSL TCTVSGGSVS SGDYYWTWIR QSPGKGLEWI
 51 GHIYYSGNTN YNPSLKSRLT ISIDTSKTQF SLKLSSVTAA DTAIYYCVRD
101 RVTGAFDIWG QGTMVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY
201 TCNVDHKPSN TKVDKTVERK CCVECPPCPA PPVAGPSVFL FPPKPKDTLM
251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV
301 VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP
351 PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG
401 SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK[1]
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[1] The Lysine (K) residue encoded at the C-terminus of the heavy chain (identified with underlining) is removed during production in CHO cells and is not present to a significant extent in the final product.

Vectibix Light Chain

```
  1 DIQMTQSPSS LSASVGDRVT ITCQASQDIS NYLNWYQQKP GKAPKLLIYD
 51 ASNLETGVPS RFSGSGSGTD FTFTISSLQP EDIATYFCQH FDHLPLAFGG
101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
```

Panitumumab has an approximate molecular weight of 147 kDa.

Vectibix™ is formulated as a sterile liquid that contains the active ingredient, sodium chloride, sodium acetate, and water. A copy of the package insert for Vectibix™ is attached for the convenience of the Office (Attachment C).

(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505.

(3) The approved product Vectibix™ received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on September 27, 2006. A copy of the approval letter is attached (Attachment D).

(4) The active ingredient in Vectibix™ is panitumumab. On information and belief, panitumumab has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to its approval by the Food and Drug Administration on September 27, 2006.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on November 25, 2006 (a Saturday). Filing on or before Monday November 27, 2006 is timely.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Aya Jakobovits, Xiao-Dong Yang, Michael Gallo, Xiao-Chi Jia

Patent No.: 6,235,883

Issue Date: May 22, 2001

Expiration Date: May 5, 2017

(7) A true copy of the patent is attached (Attachment E).

(8) No disclaimer, reexamination certificate, or Certificate of Correction has been issued on this patent. A copy of a record of maintenance fee payments under 35 U.S.C. § 41(b) is attached (Attachment F).

(9) U.S. Patent No. 6,235,883 claims isolated antibodies. At least claim 15 is the applicable claim directed to the approved product. The following description demonstrates the manner in which at least claim 15 reads on the approved product.

Claim 15 recites "An isolated antibody that is capable of binding epidermal growth factor receptor comprising a heavy chain variable region comprising a contiguous sequence from CDR1 through CDR3 as represented in SEQ ID NO:37." *See* Fig. 29. The active ingredient in the approved product is an isolated antibody that is capable of binding epidermal growth factor receptor comprising a heavy chain variable region comprising the contiguous sequence from CDR1 through CDR3 that is illustrated in SEQ ID No:37. More particularly, the heavy chain of the active ingredient comprises the following contiguous sequence from CDR1 through CDR3 that is illustrated in SEQ ID No:37:

SGDYYWTWIRQSPGKGLEWIGHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTA
ADTAIYYCVRDRVTGAFDI.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

An Investigational New Drug (IND) Application, IND No. 8382, was filed with the FDA on May 15, 1999, and was received at the FDA on May 19, 1999. The IND became effective on June 19, 1999.

A Biologics Licensing Application (BLA), BLA No. 125147/0, was initially submitted on December 15, 2005.

The Biologics Licensing Application was approved and licensed under Department of Health and Human Services U.S. License No. 1080, on September 27, 2006.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to Vectibix™ and the dates applicable to these significant activities are set forth in a chronology of events in Attachment G.

(12)(i) Applicant is of the opinion that U.S. Patent 6,235,883 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent 6,235,883 claims the active ingredient in Vectibix™.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent 6,235,883 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 6,235,883 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The product Vectibix™ has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of Vectibix™ after the regulatory review period is the first permitted commercial marketing or use under the Federal Food Drug and Cosmetic Act under which such regulatory review occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for Vectibix™.

(12)(ii) The length of the extension of patent term of U.S. Patent 6,235,883 claimed by Applicant is that period authorized by 35 U.S.C. § 156(c) which has been calculated to be 1122 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.779 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(5)(B) began on June 19, 1999 and ended September 27, 2006, which is a total of 2659 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(5)(B)(i), the "Testing Period," began on June 19, 1999 and ended on December 15, 2005, which is 2372 days; and

(2) The period of review under 35 U.S.C. § 156(g)(5)(B)(ii), the "Approval Period," began on December 15, 2005 and ended on September 27, 2006 which is a total of 287 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (2659 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (May 22, 2001) which is 703 days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) less the number of days determined in subparagraph 12(ii)(b)(1) above (one-half of 1669) which is 834 days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (1122) when added to the original term of the patent (May 5, 2017) would result in the date of May 31, 2020.

(d) Fourteen (14) years when added to the date of issuance of a license under the Federal Food Drug and Cosmetic Act (September 27, 2006) would result in the date of September 27, 2020;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is May 31, 2020;

(f) Since the patent was not issued before September 24, 1984 and since no request for an investigational new drug application under the Federal Food, Drug, and Cosmetic Act was submitted before September 24, 1984, the period of extension may not exceed five years from the original expiration date of May 5, 2017. Five years when added to the original expiration date of the patent would result in the date of May 5, 2022.

(g) The earlier date as determined by sub-paragraphs (12)(ii)(e) and (12)(ii)(f) is May 31, 2020.

(13) Applicant acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this application is attached as a check in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Charles E. Van Horn
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
Customer No. 22,852
901 New York Avenue, N.W.
Washington, D.C. 20001-4413
Phone: 202-408-4072
Fax: 202-408-4400

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and two (2) copies thereof (Attachment H).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Steven J. Scott, Reg. No. 43,911, for

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 22, 2006

Attachments:
Check for $1,120.00
Assignments (Attachment A)
Power of Attorney (Attachment B)
Package Insert (Attachment C)
Approval Letter (Attachment D)
U.S. Patent 6,235,883 (Attachment E)
Receipt of Maintenance Fee Payments (Attachment F)
Chronology of Regulatory Review Period (Attachment G)
Certification of Copies of Application Papers (Attachment H)

EXHIBIT B

Vectibix™ (panitumumab)

For Intravenous Use Only

WARNING

Dermatologic Toxicity: Dermatologic toxicities, related to Vectibix™ blockade of EGF binding and subsequent inhibition of EGFR-mediated signaling pathways, were reported in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Vectibix™ monotherapy. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Severe dermatologic toxicities were complicated by infection including sepsis, septic death, and abscesses requiring incisions and drainage. Withhold or discontinue Vectibix™ and monitor for inflammatory or infectious sequelae in patients with severe dermatologic toxicities (see **WARNINGS: Dermatologic, Mucosal, and Ocular Toxicity**; **ADVERSE REACTIONS: Dermatologic, Mucosal, and Ocular Toxicity**; and **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Dermatologic Toxicity***).

Infusion Reactions: Severe infusion reactions occurred with the administration of Vectibix™ in approximately 1% of patients. Severe infusion reactions were identified by reports of anaphylactic reaction, bronchospasm, fever, chills, and hypotension (see **WARNINGS: Infusion Reactions** and **ADVERSE REACTIONS: Infusion Reactions**). Although fatal infusion reactions have not been reported with Vectibix™, fatalities have occurred with other monoclonal antibody products. Stop infusion if a severe infusion reaction occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix™ (see **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Infusion Reactions***).

DESCRIPTION

Vectibix™ (panitumumab) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human Epidermal Growth Factor Receptor (EGFR). Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

Vectibix™ (panitumumab) is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates. Each single-use 5 mL vial contains 100 mg of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

The EGFR is a member of a subfamily of type I receptor tyrosine kinases, including EGFR (HER1, c-ErbB-1), HER2/neu, HER3, and HER4. EGFR is a transmembrane glycoprotein that is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Overexpression of EGFR is also detected in many human cancers, including those of the colon and rectum. Interaction of EGFR with its normal ligands (eg, EGF, transforming growth factor-alpha) leads to phosphorylation and activation of a series of intracellular tyrosine kinases, which in turn regulate transcription of molecules involved with cellular growth and survival, motility, proliferation, and transformation.

Panitumumab binds specifically to EGFR on both normal and tumor cells, and competitively inhibits the binding of ligands for EGFR. Nonclinical studies show that binding of panitumumab to the EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production, and internalization of the EGFR. In vitro assays and in vivo animal studies demonstrate that panitumumab inhibits the growth and survival of selected human tumor cell lines expressing EGFR.

Human Pharmacokinetics

Vectibix™ administered as a single agent exhibits nonlinear pharmacokinetics.

Following a single-dose administration of panitumumab as a 1-hour infusion, the area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner and clearance (CL) of panitumumab decreased from 30.6 to 4.6 mL/day/kg as the dose increased from 0.75 to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increases in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean (± SD) peak and trough concentrations of 213 ± 59 and 39 ± 14 mcg/mL, respectively. The mean (± SD) $AUC_{0\text{-}tau}$ and CL were 1306 ± 374 mcg•day/mL and 4.9 ± 1.4 mL/kg/day, respectively. The elimination half-life was approximately 7.5 days (range: 3.6 to 10.9 days).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on Vectibix™ pharmacokinetics. Results suggest that age (21–88 years), gender, race (15% nonwhite), mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab.

No formal pharmacokinetic studies of panitumumab have been conducted in patients with renal or hepatic impairment.

Vectibix™ has not been studied in pediatric patients.

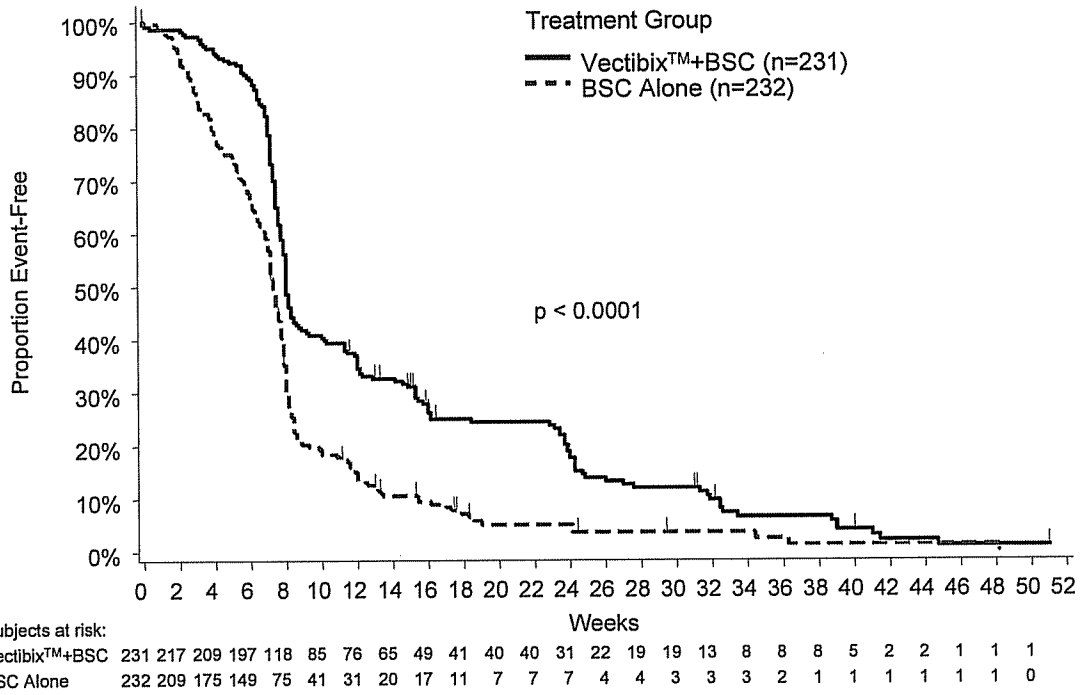
CLINICAL STUDIES

The safety and efficacy of Vectibix™ were studied in an open-label, multinational, randomized, controlled trial of 463 patients with EGFR-expressing, metastatic carcinoma of the colon or rectum (mCRC). Patients were required to have progressed on or following treatment with a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan; this was confirmed by an independent review committee (IRC) for 75% of the patients. All patients were required to have EGFR expression defined as at least 1+ membrane staining in ≥ 1% of tumor cells by the Dako EGFR pharmDx® test kit. Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus best supportive care (BSC) (n = 231) or BSC alone (n = 232) until investigator-determined disease progression. Randomization was stratified based on ECOG performance status (0–1 vs 2) and geographic region (western Europe, eastern/central Europe, or other). Upon investigator-determined disease progression, patients in the BSC-alone arm were eligible to receive panitumumab and were followed until disease progression was confirmed by the IRC. The analyses of progression-free survival (PFS), objective response, and response duration were based on events confirmed by the IRC that was masked to treatment assignment.

Among the 463 patients, 63% were male, the median age was 62 years, 40% were 65 years or older, 99% were Caucasian, 86% had a baseline ECOG performance status of 0 or 1, and 67% had colon cancer. The median number of prior therapies for metastatic disease was 2.4. The membrane-staining intensity for EGFR was 3+ in 19%, 2+ in 51%, and 1+ in 30% of patients' tumors. The percentage of tumor cells with EGFR membrane staining in the following categories of > 35%, > 20%–35%, 10%–20%, and 1%–< 10% was 38%, 8%, 31%, and 22%, respectively.

Based upon IRC determination of disease progression, a statistically significant prolongation in PFS was observed in patients receiving Vectibix™ compared to those receiving BSC alone. The mean PFS was 96 days in the Vectibix™ arm and 60 days in the BSC-alone arm. Results are presented in Figure 1 below.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival Time as Determined by the IRC



In a series of sensitivity analyses, including one adjusting for potential ascertainment bias, ie, assessment for progressive disease at a nonstudy specified time point, PFS was still significantly prolonged among patients receiving Vectibix™ as compared to patients receiving BSC alone.

Of the 232 patients randomized to BSC alone, 75% of patients crossed over to receive Vectibix™ following investigator determination of disease progression; the median time to cross over was 8.4 weeks (0.3–26.4 weeks).

There were 19 partial responses identified by the IRC in patients randomized to Vectibix™ for an overall response of 8% (95% CI: 5.0%, 12.6%). No patient in the control arm had an objective response identified by the IRC. The median duration of response was 17 weeks (95% CI: 16 weeks, 25 weeks). There was no difference in overall survival observed between the study arms.

EGFR Expression and Response

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR expression; these are the only patients studied and for whom benefit has been shown (see **INDICATIONS AND USAGE** and **PRECAUTIONS: EGF Receptor Testing**). EGFR tumor expression was determined using the Dako EGFR pharmDx® test kit. Specimens were scored based on the percentage of cells expressing EGFR and staining intensity (3+, 2+, and 1+). Exploratory univariate analyses assessing the relationship between EGFR expression and PFS did not suggest that the PFS benefit differed as a function of EGFR staining intensity or percentage of EGFR-expressing tumor cells.

INDICATIONS AND USAGE

Vectibix™ is indicated as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. (See **WARNINGS: Increased Toxicity with Combination Chemotherapy**).

The effectiveness of Vectibix™ as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on progression-free survival (see **CLINICAL STUDIES**). Currently no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Vectibix™.

CONTRAINDICATIONS

None known.

WARNINGS

Dermatologic, Mucosal, and Ocular Toxicity

Weekly administration of panitumumab to cynomolgus monkeys for 4 to 26 weeks resulted in dermatologic findings, including dermatitis, pustule formation and exfoliative rash, and deaths secondary to bacterial infection and sepsis at doses of 1.25 to 5-fold higher (on a mg/kg basis) than the recommended human dose.

In the randomized, controlled clinical trial of Vectibix™, dermatologic toxicities, related to Vectibix™ blockade of EGF binding and subsequent inhibition of EGFR-mediated signaling pathways, were reported in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 16% of patients with mCRC receiving Vectibix™. The clinical manifestations included, but were not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported. Toxicity involving gastrointestinal mucosa, eye, and nail was also reported (see **BOXED WARNING: Dermatologic Toxicity**; **ADVERSE REACTIONS: Dermatologic, Mucosal, and Ocular Toxicity**; and **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Dermatologic Toxicity***).

Infusion Reactions

In the randomized, controlled clinical trial of Vectibix™, 4% of patients experienced infusion reactions, and in 1% reactions were graded as severe (NCI-CTC grade 3–4).

Across all clinical studies, severe infusion reactions occurred with the administration of Vectibix™ in approximately 1% of patients. Severe infusion reactions were identified by reports of anaphylactic reaction, bronchospasm, fever, chills, and hypotension (see **BOXED WARNING: Infusion Reactions** and **ADVERSE REACTIONS: Infusion Reactions**). Although fatal infusion reactions have not been reported with Vectibix™, fatalities have occurred with other monoclonal antibody products. Stop infusion if a severe infusion reaction

occurs. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix™ (see **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Infusion Reactions***).

Increased Toxicity with Combination Chemotherapy

Vectibix™ is not indicated for use in combination with chemotherapy with or without bevacizumab. In an interim analysis of a randomized (1:1) clinical trial of patients with previously untreated metastatic colorectal cancer, the addition of Vectibix™ to the combination of bevacizumab and chemotherapy, resulted in decreased progression-free survival (n=947) and increased incidence of NCI-CTC grade 3-5 (87% vs. 72%) adverse reactions (n=926). All patients received bevacizumab; 86% received an oxaliplatin fluoroyrimidine-based regimen and 14% received an irinotecan-fluoropyrimidine-based regimen. NCI-CTC grade 3-4 adverse drug reactions occurring at a higher rate in Vectibix™ treated patients included rash/dermatitis/acneiform (26% vs. 1%), diarrhea (23% vs. 12%), dehydration, primarily occurring in patients with diarrhea (16% vs. 5%), hypokalemia (10% vs. 4%), stomatitis/mucositis (4% vs.<1%) and hypomagnesemia (4% vs. 0). NCI-CTC grade 3-5 pulmonary embolism occurred at a higher rate in Vectibix™ treated patients (7% vs. 4%) and included fatal events in 3 (< 1%) Vectibix ™ treated patients.

As a result of the toxicities experienced, patients randomized to Vectibix™, bevacizumab and chemotherapy, received a significantly lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5FU, and/or infusional 5FU) over the first 24 weeks on study, compared with those randomized to bevacizumab and chemotherapy.

In a single arm study of 19 patients receiving Vectibix™ in combination with IFL, the incidence of NCI-CTC grade 3–4 diarrhea was 58%; in addition, grade 5 diarrhea occurred in one patient. In a single arm study of 24 patients receiving Vectibix™ plus FOLFIRI, the incidence of NCI-CTC grade 3 diarrhea was 25%.

Pulmonary Fibrosis

Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix™. Of these two cases, one, occurring in a patient with underlying idiopathic pulmonary fibrosis who received Vectibix™ in combination with chemotherapy, resulted in death from worsening pulmonary fibrosis after four doses of panitumumab. The second case was characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on the day of the 7th dose, and persistent symptoms and CT evidence of pulmonary fibrosis following the 11th dose of panitumumab as monotherapy. An additional patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia, after 23 doses of Vectibix™ in combination with chemotherapy. Following the initial fatality, patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population that may include such patients is uncertain. Permanently discontinue Vectibix™ therapy in patients developing interstitial lung disease, pneumonitis, or lung infiltrates.

Electrolyte Depletion

In the randomized, controlled clinical trial of Vectibix™, median magnesium levels decreased by 0.1 mmol/L in the panitumumab arm; hypomagnesemia (NCI-CTC grade 3 or 4) requiring oral or IV electrolyte repletion occurred in 2% of patients. Hypomagnesemia occurred 6 weeks or longer after the initiation of Vectibix™. In some patients hypomagnesemia was associated with hypocalcemia. Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of Vectibix™ therapy (see **PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring**).

PRECAUTIONS

Photosensitivity

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving Vectibix™ since sunlight can exacerbate any skin reactions that may occur.

EGF Receptor Testing

Detection of EGFR protein expression is necessary for selection of patients appropriate for Vectibix™ therapy because these are the only patients studied and for whom benefit has been shown (see **INDICATIONS AND USAGE** and **CLINICAL STUDIES: EGFR Expression and Response**). Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR expression using the Dako EGFR pharmDx® test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specific reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. [Refer to the package insert for the Dako EGFR pharmDx® test kit, or other test kits approved by FDA, for identification of patients eligible for treatment with Vectibix™ and for full instructions on assay performance.]

Laboratory Tests: Electrolyte Monitoring

Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia, during and for 8 weeks after the completion of Vectibix™ therapy. Institute appropriate treatment, eg, oral or IV electrolyte repletion, as needed (see **WARNINGS: Electrolyte Depletion**).

Information for Patients

Patients must be informed of the possible adverse effects of Vectibix™, including dermatologic toxicity, infusion reactions, pulmonary fibrosis, and potential embryofetal lethality. Instruct patients to report skin and ocular changes, and dyspnea to a healthcare professional. Advise patients that periodic monitoring of electrolyte levels is required (see **BOXED WARNING; WARNINGS; ADVERSE REACTIONS; PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility**; and **PRECAUTIONS: Pregnancy Category C**).

Drug Interactions

No formal drug-drug interaction studies have been conducted with Vectibix™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: No carcinogenicity data for panitumumab are available in animals or humans.

Mutagenesis: The mutagenic potential of panitumumab has not been evaluated in vitro or in vivo.

Impairment of Fertility: Vectibix™ may impair fertility in women of childbearing potential. Prolonged menstrual cycles and/or amenorrhea were observed in normally cycling, female cynomolgus monkeys following weekly doses of panitumumab of 1.25 to 5-fold greater than the recommended human dose (based on body weight). Menstrual cycle irregularities in panitumumab-treated, female cynomolgus monkeys were accompanied by both a decrease and delay in peak progesterone and 17β-estradiol levels. Normal menstrual cycling resumed in most animals after discontinuation of panitumumab treatment. A no-effect level for menstrual cycle irregularities and serum hormone levels was not identified.

The effects of Vectibix™ on male fertility have not been studied. However, no adverse effects were observed microscopically in reproductive organs from male cynomolgus monkeys treated for 26 weeks with panitumumab at doses of up to approximately 5-fold the recommended human dose (based on body weight).

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. However, EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Vectibix™ treatment was associated with significant increases in embryolethal or abortifacient effects in pregnant cynomolgus monkeys when administered weekly during the period of organogenesis (gestation day [GD] 20–50), at doses approximately 1.25 to 5-fold greater than the recommended human dose (by body weight). There were no fetal malformations or other evidence of teratogenesis noted in the offspring. While no panitumumab was detected in serum of neonates from panitumumab-treated dams, anti-panitumumab antibody titers were present in 14 of 27 offspring delivered at GD 100. Therefore, while no teratogenic effects were observed in panitumumab-treated monkeys, panitumumab has the potential to cause fetal harm when administered to pregnant women.

Human IgG is known to cross the placental barrier; therefore, Vectibix™ may be transmitted from the mother to the developing fetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Vectibix™ and for 6 months following the last dose of Vectibix™. If Vectibix™ is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential risk for loss of the pregnancy or potential hazard to the fetus.

Nursing Mothers

Studies have not been conducted to assess the secretion of Vectibix™ in human milk. Because human IgG is secreted into human milk, panitumumab might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. Women must be advised to discontinue nursing during treatment with Vectibix™ and for 2 months after the last dose of Vectibix™.

Pediatric Use

The safety and effectiveness of Vectibix™ have not been established in pediatric patients.

Geriatric Use

Of 229 patients with mCRC who received Vectibix™ in the randomized, controlled study, 96 (42%) were ≥ age 65. Although the clinical study did not include a sufficient number of geriatric patients to determine whether they respond differently from younger patients, there were no apparent differences in safety and effectiveness of Vectibix™ between these patients and younger patients.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates in the clinical studies of a drug cannot be directly compared to rates in clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Safety data are available from 15 clinical trials in which 1467 patients received Vectibix™; of these, 1293 received Vectibix™ monotherapy and 174 received Vectibix™ in combination with chemotherapy. The most common adverse events observed in clinical studies of Vectibix™ (n = 1467) were skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration. The most serious adverse events observed were pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. Adverse events requiring discontinuation of Vectibix™ were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

The data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix™ administered as a single agent at the recommended dose and schedule (6.0 mg/kg every 2 weeks) in 229 patients with mCRC in the randomized, controlled trial. The median number of doses was five (range one to 26 doses), and 71% of patients received eight or fewer doses. The population had a median age of 62 years (range: 27 to 82 years); 63% were male; and 99% were white with < 1% black, < 1% Hispanic, and 0% other.

Table 1. Per-Patient Incidence of Adverse Events Occurring in ≥ 5% of Patients with a Between Group Difference of ≥ 5%

	Patients Treated With Vectibix™ Plus BSC (n = 229)		BSC Alone (n = 234)	
	Grade*			
Body System	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Body as a Whole				
Fatigue	26	4	15	3
General Deterioration	11	8	4	3
Digestive				
Abdominal Pain	25	7	17	5
Nausea	23	1	16	< 1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal Inflammation	6	< 1	1	0
Metabolic/Nutritional				
Peripheral Edema	12	1	6	< 1
Hypomagnesemia (Lab)	39	4	2	0
Respiratory				
Cough	14	< 1	7	0
Skin/Appendages				
All Skin/Integument Toxicity	90	16	9	0
Skin	90	14	6	0
Erythema	65	5	1	0
Acneiform Dermatitis	57	7	1	0
Pruritus	57	2	2	0
Skin Exfoliation	25	2	0	0
Rash	22	1	1	0
Skin Fissures	20	1	< 1	0
Dry Skin	10	0	0	0
Acne	13	1	0	0
Nail	29	2	0	0
Paronychia	25	2	0	0
Other Nail Disorder	9	0	0	0
Hair	9	0	1	0
Growth of Eyelashes	6	0	0	0
Eye	15	< 1	2	0

*Version 2.0 of the NCI-CTC was used for grading toxicities. Skin toxicity was coded based on a modification of the NCI-CTCAE, version 3.0.

Dermatologic, Mucosal, and Ocular Toxicity

In the randomized, controlled clinical trial, skin-related toxicities were reported in 90% of patients receiving Vectibix™. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. Eye-related toxicities occurred in 15% of patients and included, but were not limited to:

conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced a NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients. Other nail disorders were observed in 9% of patients (see **WARNINGS: Dermatologic, Mucosal, and Ocular Toxicity**).

Median time to the development of skin/eye-related toxicity was 14 days; the time to most severe skin/eye-related toxicity was 15 days after the first dose of Vectibix™; and the median time to resolution after the last dose of Vectibix™ was 84 days. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage, were reported. Severe toxicity necessitated dose interruption in 11% of Vectibix™-treated patients (see **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Dermatologic Toxicity***).

Infusion Reactions

Infusional toxicity was defined as any event described at any time during the clinical study as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the Vectibix™ infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Of all Vectibix™-treated patients, excluding those treated with Vectibix™ in combination with carboplatin and paclitaxel, 3% (43/1336) experienced infusion reactions of which approximately 1% (6/1336) were severe (NCI-CTC grade 3–4). In one patient, Vectibix™ was permanently discontinued for a serious infusion reaction (see **DOSAGE AND ADMINISTRATION: Dose Modifications,** ***Infusion Reactions***).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Vectibix™ has been evaluated using two different screening immunoassays for the detection of anti-panitumumab antibodies: an acid dissociation bridging enzyme linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and a Biacore® biosensor immunoassay (detecting both high- and low-affinity antibodies). The incidence of binding antibodies to panitumumab (excluding predose and transient positive patients), as detected by the acid dissociation ELISA, was 2/612 (< 1%) and as detected by the Biacore® assay was 25/610 (4.1%).

For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies. Excluding predose and transient positive patients, eight of the 604 patients (1.3%) with postdose samples and 1/350 (< 1%) of the patients with follow-up samples tested positive for neutralizing antibodies.

There was no evidence of altered pharmacokinetic profile or toxicity profile between patients who developed antibodies to panitumumab as detected by screening immunoassays and those who did not.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity in an assay may be influenced by factors such as sample handling, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to panitumumab with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The highest per-infusion dose administered in clinical studies was 9 mg/kg administered every 3 weeks. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of Vectibix™ is 6 mg/kg administered over 60 minutes as an intravenous infusion every 14 days. Doses higher than 1000 mg should be administered over 90 minutes (see **DOSAGE AND ADMINISTRATION: Preparation and Administration**). Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix™ infusions.

Dose Modifications

Infusion Reactions

(see **ADVERSE REACTIONS: Infusion Reactions**)

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Immediately and permanently discontinue Vectibix™ infusion in patients experiencing severe (grade 3 or 4) infusion reactions.

Dermatologic Toxicity

(see **ADVERSE REACTIONS: Dermatologic, Mucosal, and Ocular Toxicity**)

- Withhold Vectibix™ for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue Vectibix™.
- If dermatologic toxicity improves to ≤ grade 2, and the patient is symptomatically improved after withholding no more than two doses of Vectibix™, treatment may be resumed at 50% of the original dose.
    - If toxicities recur, permanently discontinue Vectibix™.
    - If toxicities do not recur, subsequent doses of Vectibix™ may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

Preparation and Administration

Do not administer Vectibix™ as an IV push or bolus. Vectibix™ must be administered by an IV infusion pump using a low-protein-binding 0.2 μm or 0.22 μm in-line filter.

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Although Vectibix™ should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Vectibix™ should not be administered if discoloration is observed.
- Withdraw the necessary amount of Vectibix™ for a dose of 6 mg/kg.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Final concentration should not exceed 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
- Vectibix™ must be administered via infusion pump.
    - Flush line before and after Vectibix™ administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or IV solutions. Vectibix™ should not be mixed with, or administered as an infusion with, other medicinal products. No other medications should be added to solutions containing panitumumab.
    - Infuse over 60 minutes through a peripheral line or indwelling catheter. Doses higher than 1000 mg should be infused over 90 minutes.

Stability and Storage

Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since Vectibix™ does not contain preservatives, any unused portion remaining in the vial must be discarded.

The diluted infusion solution of Vectibix™ should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.

HOW SUPPLIED

Vectibix™ is supplied as a sterile, colorless, preservative-free solution containing 20 mg/mL panitumumab in a single-use vial.

Vectibix™ (panitumumab) is provided as one vial per carton.

Each 5 mL single-use vial contains 100 mg of panitumumab (20 mg/mL) (NDC 55513-954-01).

Each 10 mL single-use vial contains 200 mg of panitumumab (20 mg/mL) (NDC 55513-955-01).

Each 20 mL single-use vial contains 400 mg of panitumumab (20 mg/mL) (NDC 55513-956-01).

Rx Only

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent No. 6,235,883, as well as other patents or patents pending.

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